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Platelet Reactivity in Patients and Recurrent Events Post-Stenting

Results of the PREPARE POST-STENTING Study

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OBJECTIVES We investigated the relation of high ex vivo platelet reactivity, rapid fibrin generation, and high thrombin-induced clot strength to postdischarge ischemic events in patients undergoing percutaneous coronary intervention (PCI).

BACKGROUND High platelet reactivity and rapid fibrin generation may affect the incidence of ischemic events after PCI. However, limited data is available to link these ex vivo markers to the occurrence of events.

METHODS We measured platelet reactivity to adenosine diphosphate (ADP) by light transmittance aggregometry (LTA) in patients undergoing PCI (n = 192). Clot strength, a measure of thrombin-induced fibrin and platelet interactions, and the time to initial fibrin generation, a marker of thrombin activity, were measured by thrombelastography. The relation of these measurements to ischemic event occurrence was prospectively examined over six months.

RESULTS A total of 100% and 84% of patients were on aspirin and clopidogrel therapy, respectively, at the time of the initial event. Posttreatment ADP-induced aggregation by LTA (63 ± 12% vs. 56 ± 15%, $p = 0.02$) and clot strength (MA) were higher (74 ± 5 mm vs. 65 ± 4 mm, $p < 0.001$) and time to initial fibrin generation was shorter (4.3 ± 1.3 min vs. 5.9 ± 1.5 min, $p < 0.001$) in patients with events (n = 38). The event rates in the highest quartiles of LTA and MA were 32% and 58%, respectively.

CONCLUSIONS High platelet reactivity and clot strength, and rapid fibrin formation are novel risk factors for ischemic events after PCI. Clot strength is more predictive than ADP-induced platelet aggregation and may explain the occurrence of events despite treatment with cyclooxygenase-1 and $P2Y_{12}$ inhibitors. (J Am Coll Cardiol 2005;46:1820–6) © 2005 by the American College of Cardiology Foundation

Platelet aggregation and activation mediated by various agonists play fundamental roles in the development of ischemia in patients with coronary artery diseases (1). Activated platelets mediate vessel wall inflammation, and generation of thrombin and platelet-platelet aggregates mechanically obstruct the vessel lumen (2). These fundamental properties served as the rationale for the evaluation of dual antiplatelet therapy in two major clinical trials (3,4). The Clopidogrel for the Reduction of Events During Observation (CREDO) and Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (PCI-CURE) studies clearly demonstrated the beneficial effects of dual antiplatelet therapy after percutaneous coronary intervention in patients with unstable coronary artery syndromes and provided strong support for the clinical significance of platelet inhibition. However, recurrent ischemic events occurred in 8.5% to 8.8% of patients despite dual antiplatelet therapy (3,4).

Because ischemic events are strongly influenced by platelet-mediated events, it is logical to hypothesize that patients suffering these events will have greater ex vivo platelet reactivity than those without events despite the use of antiplatelet drugs (5). A major reason for the lack of data correlating individual platelet function to the occurrence of ischemic events is the tedious nature, labor, and expense of serial testing with conventional laboratory assays (6). Adenosine diphosphate (ADP), thromboxane A2, and thrombin are important in vivo platelet agonists (1). Among patients undergoing percutaneous coronary intervention (PCI), patients with high platelet reactivity to low concentration ADP and lowest inhibition of ADP-induced platelet aggregation had the greatest incidence of ischemic events after the procedure (7,8). In addition, the physical properties of the clot and the kinetics of thrombin-dependent fibrin generation may affect the occurrence of ischemic events. We hypothesized that high ex vivo platelet reactivity, rapid fibrin generation, and high thrombin-induced clot strength (MA) as measured by the Thrombelastograph (TEG) Hemostasis Analyzer (Haemoscope Corporation, Niles, Illinois) were risk factors for postdischarge ischemic events in patients undergoing PCI (9–12).

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Abbreviations and Acronyms

ADP = adenosine diphosphate
GP = glycoprotein
LTA = light transmittance aggregometry
MA = clot strength
PCI = percutaneous coronary intervention
PPP = platelet-poor plasma
PRP = platelet-rich plasma
R = reaction time
ROC = receiver operator curve
TEG = thrombelastograph
TVR = target vessel revascularization

METHODS

Patients. The Investigational Review Board at Sinai Hospital of Baltimore approved this study. Consecutive patients undergoing nonemergent coronary stenting provided informed consent before the procedure. Study inclusion required that patients had to undergo percutaneous revascularization and be discharged from the hospital. Patients who provided informed consent but received coronary bypass surgery for revascularization were excluded. All patients were >18 years old. Other exclusion criteria were a history of bleeding diathesis, acute myocardial infarction within 48 h, elevated cardiac markers (above upper limits normal for the respective assay), cerebrovascular event within 3 months, chronic vessel occlusion or angiographically visible thrombus, illicit drug or alcohol abuse, prothrombin time greater than 1.5× control, platelet count <100,000/mm^3, hematocrit <30%, creatinine >4.0 mg/dl, and glycoprotein (GP) IIb/IIIa inhibitor use before the procedure.

A total of 135 patients received a loading dose of clopidogrel (300 mg [n = 75], 600 mg [n = 60]) in the catheterization laboratory immediately after successful stenting. Patients on a maintenance dose of clopidogrel at the time of admission (n = 57) did not receive a loading dose. A GP IIb/IIIa inhibitor (eptifibatide, n = 92) was administered at the discretion of the treating physician. Patients not treated with GP IIb/IIIa inhibitors received unfractionated heparin to achieve an activated clotting time ≥300 s, and patients treated with a GP IIb/IIIa inhibitor achieved an activated clotting time of 200 s to 250 s. Aspirin was administered at a 81- to 325-mg daily dose for seven days before the procedure, and 325 mg was administered on the day of the procedure and daily thereafter. The maintenance dose of clopidogrel was 75 mg daily.

Blood sampling. Pretreatment blood samples were obtained in the catheterization laboratory before GP IIb/IIIa inhibitor or heparin administration through the indwelling femoral vessel sheath and transferred to vacutainer blood collecting tubes (Becton-Dickinson, Franklin Lakes, New Jersey) containing 3.8% trisodium citrate (for light transmittance aggregometry [LTA]) or 40 USP lithium heparin (for TEG assay) after discarding the first 2 to 3 ml of free flowing blood. The vacutainer tube was filled to capacity and gently inverted three to five times to ensure complete mixing of the anticoagulant. Blood samples were obtained at least 18 h after cessation of therapy in patients treated with a GP IIb/IIIa inhibitor. In the remaining patients, the discharge blood samples were obtained at least 24 h postprocedure.

LTA. Platelet aggregation was assessed as described previously (13). Briefly, the blood-citrate tubes were centrifuged at 120 *g* for 5 min to recover platelet-rich plasma (PRP) and further centrifuged at 850 *g* for 10 min to recover platelet-poor plasma (PPP). The PRP and PPP were stored at room temperature to be used within 2 h. Platelets were stimulated with 20 μM ADP, and the aggregation was assessed using a Chronolog Lumi-Aggregometer (Model 490-4D) with the Aggro/Link software package (Chronolog, Havertown, Pennsylvania). Aggregation was expressed as the maximum percent change in light transmittance from baseline, using PPP as a reference.

MA and fibrin generation time. The TEG Hemostasis Analyzer with automated analytical software provides quantitative and qualitative measurements of the physical properties of a clot (9–11). In essence, the TEG is a viscoelastic monitor that measures the degree of platelet-fibrin-mediated MA. Fibrin strands in the blood sample link a rotating sample cup with a stationary pin suspended by a torsion wire (Fig. 1). The

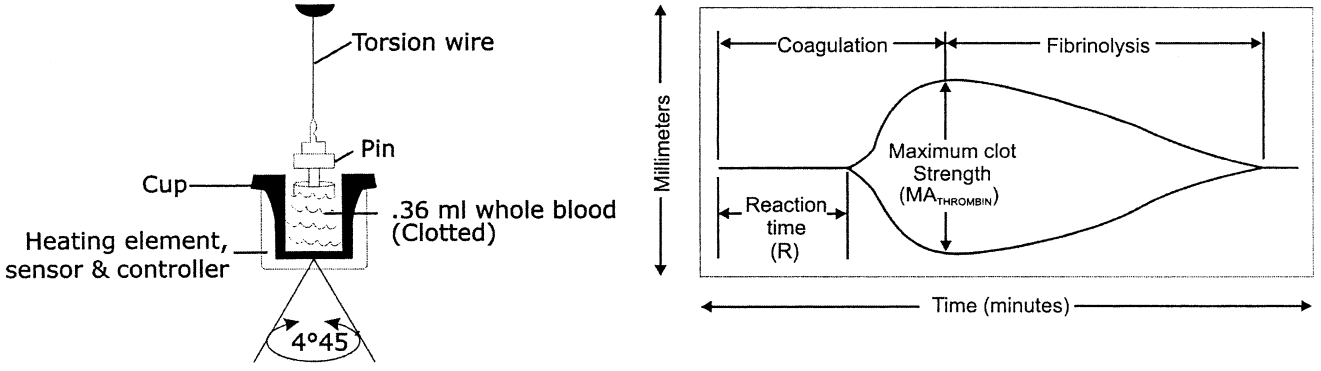

Figure 1. Schematic of thrombelastograph system: a torsion wire suspending a pin that is immersed in blood. As the clot forms while the cup is rotated 45°, the pin will rotate depending on the strength of the fibrin-platelet bonds. Signal is discharged continuously that reflects the onset of clotting (reaction time [R]) and the clot strength (MA).

Table 1. Patient Demographics

	Patients With Ischemic Events (n = 38)	Patients Without Ischemic Events (n = 154)	p Value
Age (yrs)	59 ± 10	62 ± 12	NS
Race (Caucasian) (%)	68	57	NS
Gender (male) (%)	42	60	0.05
BMI (kg/m^2)	31 ± 7	30 ± 7	NS
Risk factors/past medical history (%)			
Smoking	39	45	NS
Family history of CAD	47	32	NS
Hypertension	81	63	0.04
Hyperlipidemia	92	57	0.001
Diabetes	50	40	NS
Prior myocardial infarction	24	40	NS
Prior CABG	18	26	NS
Prior PTCA	42	39	NS
Pretreatment medications (%)			
Beta-blockers	90	81	NS
ACE inhibitors	74	61	NS
Calcium-channel blockers	21	22	NS
Lipid-lowering agents			
3A4 pathway metabolized	74	61	NS
Non-3A4 pathway metabolized	18	24	NS
Laboratory data			
WBC (× 1,000/mm^3)	7.3 ± 2.3	7.6 ± 2.4	NS
Platelets (× 1,000/mm^3)	244 ± 79	222 ± 66	NS
Hemoglobin (g/dl)	12.7 ± 2.3	13.3 ± 1.8	NS
Creatinine (g/dl)	1.1 ± 0.6	1.1 ± 0.8	NS

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; PTCA = percutaneous coronary angioplasty; WBC = white blood cells; 3A4 = hepatic cytochrome 3A4.

torque of the rotating cup is transmitted to the immersed pin. Pin movement is converted to an electrical signal by a transducer and is interpreted by the computer to create a tracing. The degree of platelet contribution to the MA through platelet-fibrin bonding directly influences the magnitude of pin movement and ultimately the amplitude of the tracing. In the present study, the maximum amplitude of the thrombin-generated clot (MA) (mm) and the time from the start of the sample run to the first significant levels of clot formation (reaction time [R]) (min) were measured (Fig.

Table 2. Procedural Characteristics

	Patients With Ischemic Events (n = 38)	Patients Without Ischemic Events (n = 154)	p Value
Length of procedure (min)	55 ± 22	62 ± 34	NS
Ejection fraction (%)	48 ± 9	52 ± 9	NS
Number of vessels treated	1.3 ± 0.5	1.3 ± 0.6	NS
Lesion morphology			
De novo (%)	87	89	NS
Culprit lesion location (%)			
LAD	40	38	NS
CX	21	25	NS
RCA	34	30	NS
SVG	5	7	NS
Stent types (%)			
Drug-eluting	75	68	NS
Bare-metal	18	29	NS
PTCA only	7	3	NS
Reference vessel diameter (mm)	3.0 ± 0.4	3.0 ± 0.5	NS
Total lesion length (mm)	21.9 ± 10.1	19.0 ± 12.2	NS
Prestenosis (%)	86	84	NS
Poststenosis (%)	5	5	NS
Procedural success (%)	95	96	NS

CX = circumflex artery; LAD = left anterior descending artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; SVG = saphenous vein graft.

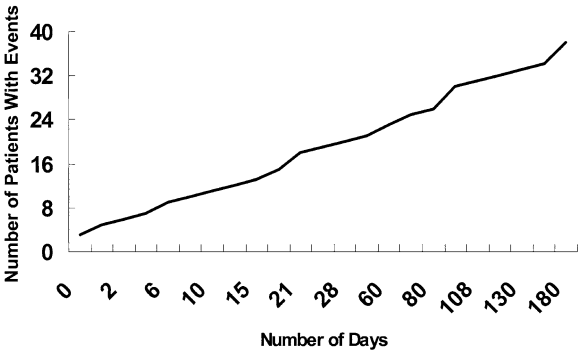

Figure 2. Graph demonstrating the time of occurrence of the first ischemic event.

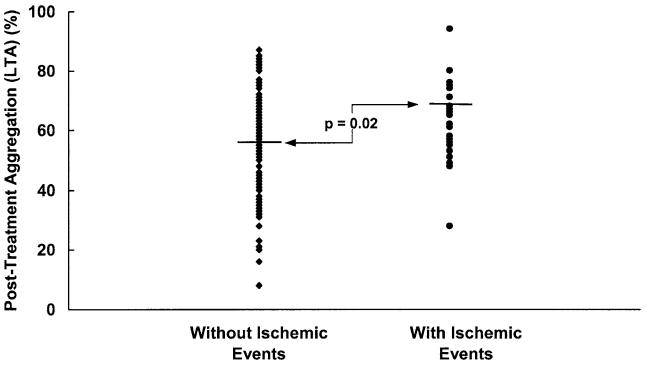

Figure 3. Adenosine-diphosphate-induced posttreatment platelet aggregation (20 μM) measured by light transmittance aggregometry (LTA) in patients without ischemic events and with ischemic events.

1). The R parameter, a measure of initial thrombin-generated fibrin formation, has been correlated with the velocity of thrombin generation (9).

Blood was analyzed according to the manufacturer's instructions; 1 ml of heparinized blood was transferred to a vial containing kaolin and mixed by inversion; 500 μl of the activated blood was then transferred to a vial containing heparinase and mixed to neutralize the heparin. The neutralized blood (360 μl) was immediately added to a heparinase-coated cup and assayed in the TEG analyzer according to the manufacturer's instructions to obtain the thrombin-induced clot.

Definitions and clinical outcomes. Patients were contacted by telephone at the end of one month and six months to determine the occurrence of adverse events. Ischemic events were defined as the occurrence of death secondary to cardiovascular cause, myocardial infarction, unstable angina, and stroke that required rehospitalization. Myocardial infarction was defined as the occurrence of ischemic symptoms and a troponin I value greater than upper limits of normal. Unstable angina was defined as the occurrence of ischemic symptoms requiring rehospitalization. A physician blinded to the study results of the patient diagnosed all end points. Patients were divided into two groups based on the occurrence of adverse ischemic events. High LTA and MA were defined as >75th percentile. Low R was defined as <25th percentile.

Statistical analysis. The linear logistic regression model was employed to fit the binary data (ischemic event = 1 and nonischemic event = 0) while comparing different quartiles. This logistic regression model was fit using SAS procedure PROC LOGISTIC (SAS Inc., Cary, North Carolina). The model is given by:

$$Logit(\mathrm{p}) = Log\{\mathrm{p}/(1-\mathrm{p})\} = \beta_0 + \beta_1 \cdot \mathrm{QUARTILE\_X}$$

where p = proportion of incidence of ischemic event, and QUARTILE_X is a factor with four quartiles of the variable X as its four levels. Appropriate pairwise comparisons were made using the corresponding contrasts to assess the difference between the two levels of the factor with respect to the proportion of ischemic events. The three variables (possible X) considered here are MA, LTA, and R.

The multiple linear logistic regression model was employed to fit binary data to compare the occurrence of difference risk factors in patients with ischemic events and without ischemic events. The logistic regression model was fit using SAS procedure PROC LOGISTIC (SAS Inc.). Odds ratio were calculated using SAS software, and receiver operator curves (ROC) were generated using MedCalc Software (Mariakerke, Belgium). Based on the normal distribution of data, the mean ± SD is reported except as otherwise noted, and $p < 0.05$ was considered significant.

RESULTS

Patients and clinical outcomes. A total of 192 patients underwent catheter-based treatment and were analyzed. All of the procedures performed were nonemergent; 36 patients

Table 3. Evaluation of Platelet Function Tests by Light Transmittance Aggregometry and TEG

	Patients With Ischemic Events	Patients Without Ischemic Events	p Value
20 μM ADP-induced pretreatment aggregation (%)	71 ± 9	73 ± 12	NS
20 μM ADP-induced post-treatment aggregation (%)	63 ± 12	56 ± 16	0.02
TEG MA pretreatment (mm)	72 ± 7	67 ± 8	<0.001
TEG MA post-treatment (mm)	74 ± 5	65 ± 4	<0.001
Reaction time pretreatment (min)	4.6 ± 2.3	4.7 ± 2.0	NS
Reaction time post-treatment (min)	4.3 ± 1.3	5.9 ± 1.5	<0.001

ADP = adenosine diphosphate; MA = clot strength; TEG = thrombelastograph.

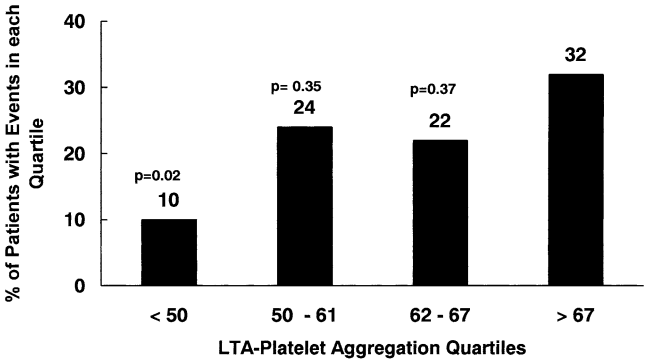

Figure 4. The observed frequency of patients with ischemic events in each quartile of light transmittance aggregometry (LTA) values is shown in the figure. The p values given in the figure indicate that the proportions of ischemic events in the first and the fourth quartiles are significantly different, whereas the proportions of ischemic events in the fourth quartile are not significantly different from the second or the third quartiles.

were admitted with unstable angina, and 11 patients had non–ST-segment elevation myocardial infarction. The remainder of the patients had stable angina. The patient demographics and procedural characteristics of patients with and without ischemic events are shown in Tables 1 and 2, respectively. There were four in-hospital ischemic events. All of these patients had myocardial infarction diagnosed by the occurrence of chest pain and increase in troponin I greater than upper limits normal. One of these patients had stent thrombosis.

Six-month follow-up data were complete in 191 of 192 patients. There were 44 events that occurred in 38 patients (20%) within six months of discharge (Fig. 2). All events occurred during aspirin therapy. Thirty-two patients were receiving aspirin and clopidogrel therapy at the time of their first event. Within one month after discharge, 20 of 191 patients (~10%) had events: myocardial infarction involving target vessel (n = 2), ischemia requiring revascularization of the prior target vessel (TVR) (n = 2 patients), ischemia involving a vessel other than the prior target vessel requiring revascularization (non-TVR) (n = 6), ischemia requiring hospitalization but not revascularization (n = 9), and stroke (n = 1). Between one and six months, 18 patients had the first occurrence of an event: death (n = 2), ischemia

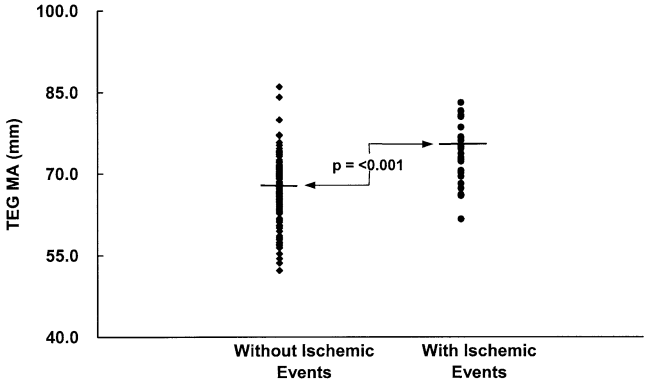

Figure 5. Post-treatment clot strength (MA) measured by thrombelastograph (TEG) in patients without ischemic events and with ischemic events.

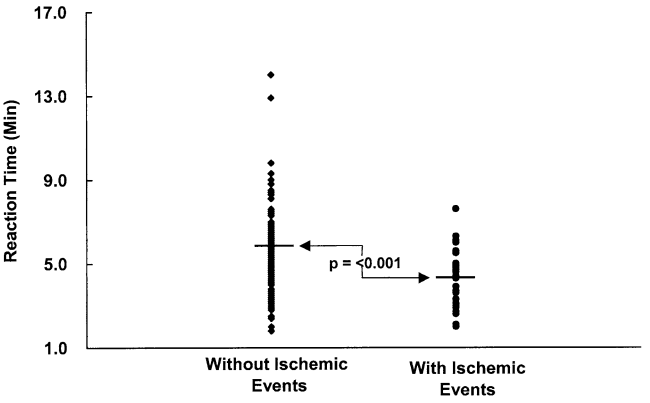

Figure 6. Post-treatment reaction time measured by thrombelastograph in patients without ischemic events and with ischemic events.

requiring TVR (n = 6), ischemia requiring non-TVR (n = 4), and ischemia requiring hospitalization but not revascularization (n = 6). Six patients had the occurrence of a second event between one and six months: coronary artery bypass grafting (n = 2), ischemia requiring TVR (n = 1), ischemia requiring non-TVR (n = 1), and ischemia requiring hospitalization but not revascularization (n = 2).

Platelet aggregation. A total of 160 patients had platelet aggregation measured by LTA, and 192 patients had blood samples analyzed by the TEG system (Table 3). Pretreatment aggregation by LTA was 71 ± 9% in patients with ischemic events and 73 ± 12% in patients without ischemic events (p = NS). Patients with ischemic events demonstrated a higher mean discharge ADP-induced platelet aggregation by LTA than patients without ischemic events (p = 0.02) (Table 3, Fig. 3). The change in mean platelet aggregation between pre- and postprocedure for the event group was 8% versus 17% for the group without events (p < 0.001). The greatest frequency of patients with ischemic events was present in the highest quartile of platelet aggregation (Fig. 4).

MA and R by TEG. Patients with ischemic events had significantly greater pre- and posttreatment MA than patients without ischemic events (p < 0.001) (Table 3, Fig. 5).

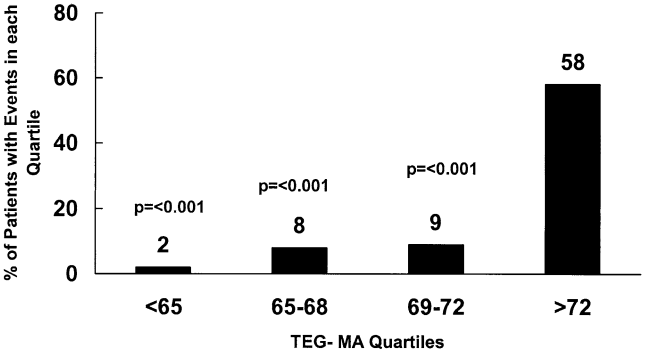

Figure 7. The observed frequency of patients with ischemic events in each quartile of clot strength (MA) values is shown in the figure. The p values given indicate that the proportion of ischemic events in each of the first three quartiles is significantly different from the proportion of ischemic events in the fourth quartile (p < 0.001). TEG = thrombelastograph.

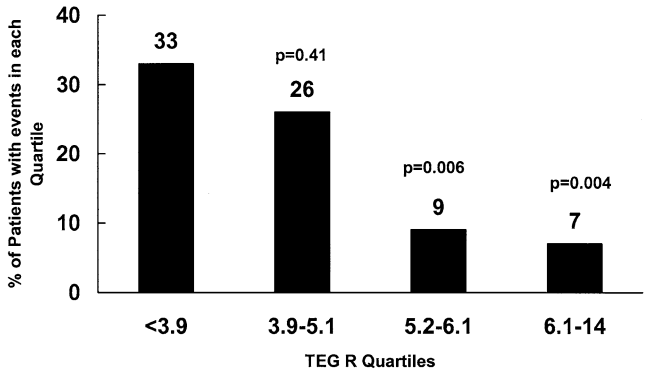

Figure 8. The observed frequency of patients with ischemic events in each quartile of reaction time (R) values is shown in the figure. The p values indicate that the proportions of ischemic events in first and the second quartiles are not significantly different (p = 0.41) whereas the proportions of ischemic events in the first quartile is significantly different from the third (p = 0.006) and the fourth quartiles (p = 0.004). TEG = thrombelastograph.

The R did not differ between groups at baseline but was significantly shorter in patients with events when measured postprocedure ($p < 0.001$) (Fig. 6). The highest quartile of MA and the lowest quartile of thrombin generation time were associated with the maximum occurrence of ischemic events (Figs. 7 and 8, respectively).

Patients with ischemic events. The occurrence of risk factors (high MA, low R, and high LTA) in patients with and without ischemic events, estimates of the parameters of the logistic regression model, odds ratios, and 95% confidence intervals are presented in Table 4. Among the 38 patients with events, only 4 patients had no risk factors at all (11%) as compared to 56% in the nonischemic group ($p < 0.0001$). The most prevalent risk factor in patients with ischemia was high MA (71%) with odds ratio estimate of 22.6 (95% confidence interval, 6.20 to 82.60), followed by a low R (42%, p = 0.05) with odds ratio estimate of 4.4 (95% confidence interval 1.00 to 19.05) and high LTA (35%, p = 0.21) with odds ratio estimate of 2.7 (95% confidence interval 0.56 to 12.96). Only 12% of patients without events demonstrated a high MA ($p < 0.0001$). The combined presence of two major risk factors, high MA and low R, in the ischemic events group was significantly higher (29%) compared to the non-ischemic events group (4%, $p < 0.0001$). The presence of all three risk factors was 100% predictive of an ischemic event.

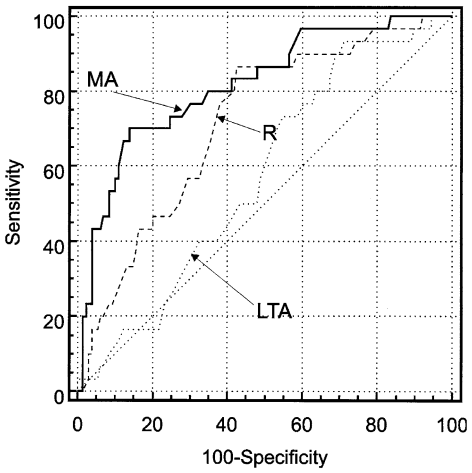

Figure 9. Combined receiver operator curve for clot strength (Thrombelastograph [TEG] MA), reaction time (TEG R), and 20 μM adenosine-diphosphate-induced posttreatment platelet aggregation (light transmittance aggregometry [LTA]). High TEG MA has 74% sensitivity and 89% specificity; low TEG R has 42% sensitivity and 79% specificity; high LTA has 37% sensitivity and 79% specificity.

The combined ROC, sensitivity, and specificity for risk factors are shown in Figure 9. A high MA was the most specific and sensitive risk factor for the occurrence of ischemic events.

DISCUSSION

The current study suggests that in addition to high ex vivo platelet reactivity to ADP, greater overall MA and rapid fibrin generation are novel risk factors for the occurrence of post-PCI ischemic events. Greater reactivity to ADP in patients with ischemic events was supported by conventional LTA, the most common measurement reported in the literature. Thrombelastograpy has never been used as a predictive tool for ischemic events after PCI but has predictive value in surgical patients as a method to determine etiologies of bleeding (9,10). In the only other study that evaluated MA as a risk factor for thrombosis, McCrath et al. (11) demonstrated that noncardiac surgical patients with ischemic events had a significantly higher MA than those without events (~73 vs. ~65 mm, respectively). These data are concordant with our study.

A low incidence of ischemic events was observed in patients within the lowest quartile of aggregation measured

Table 4. Observed Frequency (%) of Patients Without Ischemic Events and With Ischemic Events in Risk Factor Groups, Estimates of the Parameters of the Logistic Regression Model, Odds Ratio, and 95% Confidence Intervals for the Odds Ratio

	High MA	Low R	High LTA	High MA and Low R	No Risk Factor
Patients without ischemic events, n (%)	18 (12%)	31 (21%)	30 (20%)	6 (4%)	83 (56%)
Patients with ischemic events, n (%)	27 (71%)	16 (42%)	13 (35%)	11 (29%)	4 (11%)
Estimate (SE)	3.12 (0.66)	1.47 (0.75)	0.99 (0.80)	3.64 (0.72)	—
p Value	<0.0001	0.0498	0.2129	<0.0001	—
Odds ratio estimate	22.6	4.4	2.7	38.0	—
95% confidence interval for the odds ratio	6.202–82.604	1.002–19.051	0.565–12.964	9.261–156.245	—

LTA = light transmittance aggregometry; MA = clot strength; R = reaction time.

by LTA, indicating the influence of successful $P2Y_{12}$ receptor blockade in the prevention of ischemic events. Indeed, the decrease in ADP-induced platelet aggregation levels after antiplatelet therapy was less pronounced in patients with events as compared to patients without events. The change in mean platelet aggregation between pre- and postprocedure for the event group was 8% versus 17% for the group without events ($p < 0.001$). The near absence of events in patients with <50% posttreatment aggregation induced by 20 μM ADP may also suggests a therapeutic target for $P2Y_{12}$ inhibitors. More importantly, ~50% of the events occurred in patients with 25th to 75th percentile posttreatment platelet reactivity to ADP. This observation strongly suggests that agonists other than ADP play a dominant role in the genesis of ischemic events and that antiplatelet therapy directed against $P2Y_{12}$ and cyclooxygenase-1 in the current dosages is not sufficient to overcome thrombosis in selected patients.

In the current investigation, maximum MA measured by the TEG analyzer was the most sensitive and specific marker of ischemic risk and supports the central role of platelet reactivity to thrombin in recurrent ischemia post-PCI. A total of 58% of patients in the highest MA quartile developed events whereas those in the lowest two quartiles (lower quartiles) were nearly free of events. A total of 71% of the patients suffering from events were classified in the highest quartile of MA, and only 12% of patients without events were ranked in the highest quartile. Of these 12%, 76% had normal R as measured by the TEG analyzer. In ~40% of cases where the MA was high (>75th percentile), and an event occurred, the R was low (<25th percentile). When high MA was accompanied by a low R, there was an extremely high occurrence of ischemic events (odds ratio 38.0, $p < 0.0001$). These findings suggest that rapid thrombin generation often accompanies high MA. All of our data indicate that high responsiveness to thrombin (high MA) and accelerated thrombin generation (low R) are important predictive ex vivo measurements. Thus, selected patients with average ADP-induced posttreatment aggregation but with high MA and/or low R remain at risk for events.

Finally, the R significantly increased after PCI in those patients without ischemic events whereas in patients with events the mean value decreased. These findings suggest that effective clopidogrel therapy may influence thrombin generation. It has been reported that clopidogrel reduces thrombin generation (14,15).

Study limitations. Patients were not stratified before clinical events to different degrees of platelet reactivity or MA. It is uncertain whether improvements in the degree of platelet reactivity or MA before and after the procedure would help an individual patient in reducing their risk of a future ischemic event.

Conclusions. High ex vivo platelet reactivity and rapid generation of fibrin are risk factors for the development of ischemic events within six months of PCI. Moreover, MA, a marker of thrombin-induced platelet-fibrin aggregation, is more predictive than platelet reactivity to ADP. These findings may explain the occurrence of events despite treatment with cyclooxygenase-1 and $P2Y_{12}$ inhibitors. Furthermore, it suggests the need to address effective inhibition of thrombin during and after PCI. Larger scale clinical trials are warranted to evaluate these prognostic measures and their implementation for therapeutic decisions.

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REFERENCES

1. Gurbel PA, Bliden KP, Hayes KM, Tantry U. Platelet activation in myocardial ischemic syndromes. Expert Rev Cardiovasc Ther 2004;2:535–45.
2. Samara WM, Gurbel PA. The role of platelet receptors and adhesion molecules in coronary artery disease. Coron Artery Dis 2003;14:65–79.
3. Steinhubl SR, Berger PB, Mann JT, 3rd, et al., for the CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.
4. Mehta SR, Yusuf S, Peters RJ, et al., for the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
5. Gurbel PA, Samara WM, Bliden KP. Failure of clopidogrel to reduce platelet reactivity and activation following standard dosing in elective stenting: implications for thrombotic events and restenosis. Platelets 2004;15:95–9.
6. Gurbel PA, Serebruany VL. Adhesion molecules, platelet activation, and cardiovascular risk. Am Heart J 2002;143:196–8.
7. Kabbani SS, Watkins MW, Ashikaga T, et al. Platelet reactivity characterized prospectively: a determinant of outcome 90 days after percutaneous coronary intervention. Circulation 2001;104:181–6.
8. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171–5.
9. Rivard GE, Brummel-Ziedins KE, Mann KG, Fan L, Hofer A, Cohen E. Evaluation of the profile of thrombin generation during the process of whole blood clotting as assessed by thromboelastography. J Thromb Haemost 2005;3:2039–43.
10. Khurana S, Mattson JC, Westley S, O'Neill WW, Timmis GC, Safian RD. Monitoring platelet glycoprotein IIb/IIIa-fibrin interaction with tissue factor-activated thromboelastography. J Lab Clin Med 1997;130:401–11.
11. McCrath D, Cerboni E, Hirsh A, Frumento RJ, Bennet-Guerrero E. Association of thrombelastography (MA) and thrombotic complications after major non-cardiac surgery. Anesth Analag 2003;96:SCA1–141.
12. Kawasaki J, Katori N, Kodaka M, Miyao H, Tanaka K. Electron microscopic evaluations of clot morphology during thromboelastography. Anesth Analg 2004;99:1440–4.
13. Samara WM, Bliden KP, Tantry US, Gurbel PA. The difference between clopidogrel responsiveness and posttreatment platelet reactivity. Thromb Res 2005;115:89–94.
14. Wegert W, Graff J, Kaiser D, Breddin HK, Klinkhardt U, Harder S. Effects of antiplatelet agents on platelet-induced thrombin generation. Int J Clin Pharmacol Ther 2002;40:135–41.
15. Herault JP, Dol F, Gaich C, Bernat A, Herbert JM. Effect of clopidogrel on thrombin generation in platelet-rich plasma in the rat. Thromb Haemost 1999;81:957–60.